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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/308,830	08/04/1999	PATRICK M. SCHLIEVERT	600.346USWO	6704

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[REDACTED] EXAMINER

ZEMAN, ROBERT A.

[REDACTED] ART UNIT [REDACTED] PAPER NUMBER

1645

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21

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)
	09/308,830	SCHLIEVERT ET AL.
	Examin r Robert A. Zeman	Art Unit 1645

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) Responsive to communication(s) filed on 03 October 2001.

2a) This action is FINAL. 2b) This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4) Claim(s) 30-101 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5) Claim(s) _____ is/are allowed.

6) Claim(s) 30-101 is/are rejected.

7) Claim(s) _____ is/are objected to.

8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) The proposed drawing correction filed on _____ is: a) approved b) disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.

12) The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) All b) Some * c) None of:

1. Certified copies of the priority documents have been received.
2. Certified copies of the priority documents have been received in Application No. _____.
3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) The translation of the foreign language provisional application has been received.

15) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)	4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____ .
2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)	5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)
3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) <u>19</u> .	6) <input type="checkbox"/> Other: _____ .

DETAILED ACTION

All pending rejections are withdrawn. All bases for rejection are outlined below.

Election/Restrictions

Applicant's election with traverse of Group I in Paper No. 22 is acknowledged. However, upon further consideration the claims of Groups I-IV are rejoined. Consequently, claims 30-101 are pending and currently under examination.

Claim Rejections - 35 USC § 112, Written Description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, first paragraph "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Claims 30-47, 50-74, 77-88 and 91-99 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant claims are drawn to mutants of SPE-A and vaccines comprising said vaccines. Said mutants, as claimed, comprise a multitude of mutations in the "wild-type" SPE-A sequence. However, since no baseline sequence is provided for the "wild-type" SPE-A none of these mutant proteins meet the

written description provision of 35 USC 112, first paragraph. The specification provides insufficient written description to support the genus encompassed by the claims. Applicant has indicated that Figure 3 contains a sequence for wild type SPE-A. However, Applicant has not included said sequence in his claim language. Since, as indicated by Applicant on page 12 in Paper No. 17, there is variability between wild-type SPE-A sequences, the specification does not support the genus (all mutants derived from all possible wild type SPE-A sequences) encompassed by the rejected claims.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

Moreover, the skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides and/or proteins, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404. 1405 held that: ...To fulfill the written description requirement, a patent specification must describe an invention and does so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines Inc.* , 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); *In re Gosteli* , 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures,

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diagrams, formulas, etc., that set forth the claimed invention." *Lockwood*, 107 F.3d at 1572, 41 USPQ2d at 1966.

An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. *Fiers v. Revel*, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." *Id.* at 1170, 25 USPQ2d at 1606.

The name cDNA is not itself a written description of that DNA; it conveys no distinguishing information concerning its identity. While the example provides a process for obtaining human insulin-encoding cDNA, there is no further information in the patent pertaining to that cDNA's relevant structural or physical characteristics; in other words, it thus does not describe human insulin cDNA. Describing a method of preparing a cDNA or even describing the protein that the cDNA encodes, as the example does, does not necessarily describe the cDNA itself. No sequence information indicating which nucleotides constitute human cDNA appears in the patent, as appears for rat cDNA in Example 5 of the patent. Accordingly, the specification does not provide a written description of the invention of claim 5.

35 U.S.C. First Paragraph, Enablement Rejection

Claims 30-45, 50-72, 77-86 and 91-97 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for SPE-A mutants designated SPE-A N20D, SPE-A C87S, SPE-A C90S, SPE-A C98S, SPE-A K157E, SPE-A S195A, SPE-A K16N, SPE-A D45N, SPE-A N20D/C98S, SPE-A N20D/K157E and SPE-A N20D/D45N/C98S does not reasonably provide enablement for the myriads of other polypeptides species claimed. The specification is enabling only for claims limited to mutants represented by the aforementioned designations and does not enable any person skilled in the art to which it pertains or with which it is most nearly connected, to make/use the invention commensurate in scope with these claims.

The instant claims are drawn to mutants of SPE-A. Said mutants, as claimed, may comprise a multitude of mutations in the "wild-type" SPE-A sequence. However, since no baseline sequence is

provided for the "wild-type " SPE-A one of skill in the art would not be able to make and use the claimed SPE-A mutants. Applicant has indicated that Figure 3 contains a sequence for wild type SPE-A. However, Applicant has not included said sequence in his claim language. Since, as indicated by Applicant on page 12 in Paper No. 17, there is variability between wild-type SPE-A sequences, the specification does not support the genus (all mutants derived from all possible wild type SPE-A sequences) encompassed by the rejected claims.

Protein chemistry is probably one of the most unpredictable areas of biotechnology Consequently, the effects of sequence dissimilarities upon protein structure and function cannot be predicted. Bowie et al (Science, 1990, 257:1306-1310) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instructions of the genome and further teaches that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. (column 1, page 1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (column 2, page 1306). The sensitivity of proteins to alterations of even a single amino acid in a sequence are exemplified by Burgess et al (J. of Cell Bio. 111:2129-2138, 1990) who teach that replacement of a single lysine reside at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein and by Lazar et al. (Molecular and Cellular Biology, 1988, 8:1247-1252) who teach that in transforming growth factor alpha, replacement of aspartic acid at position 47

with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen. These references demonstrate that even a single amino acid substitution will often dramatically affect the biological activity and characteristics of a protein. Clearly, mutant proteins based on an unknown sequence could not be predicted. Additionally, Bork (Genome Research, 2000,10:398-400) clearly teaches the pitfalls associated with comparative sequence analysis for predicting protein function because of the known error margins for high-throughput computational methods. Bork specifically teaches that computational sequence analysis is far from perfect, despite the fact that sequencing itself is highly automated and accurate (p. 398, column 1). One of the reasons for the inaccuracy is that the quality of data in public sequence databases is still insufficient. This is particularly true for data on protein function. Protein function is context dependent, and both molecular and cellular aspects have to be considered (p. 398, column 2). Conclusions from the comparison analysis are often stretched with regard to protein products (p. 398, column 3). Further, although gene annotation via sequence database searches is already a routine job, even here the error rate is considerable (p. 399, column 2). Most features predicted with an accuracy of greater than 70% are of structural nature and, at best, only indirectly imply a certain functionality (see legend for table 1, page 399). As more sequences are added and as errors accumulate and propagate it becomes more difficult to infer correct function from the many possibilities revealed by database search (p. 399, paragraph bridging columns 2 and 3). The reference finally cautions that although the current methods seem to capture important features and explain general trends, 30% of those features are missing or predicted wrongly. This has to be kept in mind when processing the results further (p. 400, paragraph bridging cols 1 and 2). Clearly, given not only the teachings of Bowie et al., Lazar et al. and Burgess et al. but also the limitations and pitfalls of using computational sequence analysis and the unknown effects of alternative splicing, post translational modification and cellular context on protein function as taught by

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Bork, the claimed proteins could not be predicted based on an unknown sequence. Further, even if a given polypeptide possesses all the structural limitations of the claimed invention, neither the specification nor any art of record teaches what that polypeptide is, what it does, does not teach a relationship to any specific disease or establish any involvement of the polypeptide in the etiology of any specific disease or teach which fragments might be active or which derivatives would function as claimed in a pharmaceutical composition. Clearly, it could not be predicted that polynucleotide, or a variant, that encodes a protein that shares only partial homology with a disclosed protein or that a protein that is encoded by a "variant" of a given SEQ ID NO: will function in a given manner. Reasonable correlation must exist between the scope of the claims and scope of enablement set forth, and it cannot be predicted from the disclosure how to make/use mutant SPE-A proteins. In view of the above, one of skill in the art would be forced into undue experimentation to practice the claimed invention.

Claims 46, 48, 73, 75, 87, 89, 98 and 100 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for SPE-A vaccines designated SPE-A N20D, SPE-A D45N, SPE-A N20D/C98S, SPE-A N20D/K157E and SPE-A N20D/D45N/C98S does not reasonably provide enablement for the myriads of other polypeptides species claimed for use as a vaccine. The specification is enabling only for claims limited to mutants represented by the aforementioned designations and does not enable any person skilled in the art to which it pertains or with which it is most nearly connected, to make/use the invention commensurate in scope with these claims.

The instant claims are drawn to mutants of SPE-A and their use as vaccines. Said mutants, as claimed, may comprise a multitude of mutations in the "wild-type" SPE-A sequence. The rejected claims are drawn to vaccines comprising SPE-A mutants and the prophylactic use of said vaccines. To be a prophylactic composition, the composition must elicit protective immunity,

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demonstrable by pathogen challenge experiments in a reasonable model system. The specification, as filed, does not set forth which mutants (other than SPE-A N20D, SPE-A D45N, SPE-A N20D/C98S, SPE-A N20D/K157E and SPE-A N20D/D45N/C98S) provide any sort of protective immunity in any model system that can be extrapolated to humans. While the skill in the art of immunology is high, to date, prediction of protective immunity for any given composition in any given animal is quite unpredictable. Given the lack of success in the art, the lack of working examples and the unpredictability of the generation of protective immunity, the specification, as filed, does not provide enablement for vaccines and use of said vaccines against a biological activity of wild-type SPE-A. Additionally, since no baseline sequence is provided for the "wild-type" SPE. Applicant has indicated that Figure 3 contains a sequence for wild type SPE-A. However, Applicant has not included said sequence in his claim language. Since, as indicated by Applicant on page 12 in Paper No. 17, there is variability between wild-type SPE-A sequences, the specification does not support the genus (all mutants derived from all possible wild type SPE-A sequences) encompassed by the rejected claims.

Claims 47, 49, 74, 76, 88, 90, 99 and 101 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for pharmaceutical compositions comprising mutant SPE-A proteins designated SPE-A N20D, SPE-A D45N, SPE-A N20D/C98S, SPE-A N20D/K157E and SPE-A N20D/D45N/C98S does not reasonably provide enablement for the myriads of other polypeptide species claimed for use as a therapeutic (pharmaceutical) composition. The specification is enabling only for claims limited to mutants represented by the aforementioned designations and does not enable any person skilled in

the art to which it pertains or with which it is most nearly connected, to make/use the invention commensurate in scope with these claims.

The instant claims are drawn to mutants of SPE-A and their use as therapeutic (pharmaceutical) compositions. Said mutants, as claimed, may comprise a multitude of mutations in the “wild-type” SPE-A sequence. The rejected claims are drawn to therapeutic (pharmaceutical) compositions comprising SPE-A mutants and their use. To be considered therapeutic, the administration of a given compound must be beneficial to the subject to which is administered. The specification, as filed, does not set forth which mutants (other than SPE-A N20D, SPE-A D45N, SPE-A N20D/C98S, SPE-A N20D/K157E and SPE-A N20D/D45N/C98S) provide any sort benefit to the recipient of said mutant. While the skill in the art of immunology is high, to date, prediction of whether a given composition would be therapeutic is quite unpredictable. Given the lack of success in the art, the lack of working examples and the unpredictability of a therapeutic response, the specification, as filed, does not provide enablement for all the claimed compositions and their use as a therapeutic (pharmaceutical) composition. Additionally, since no baseline sequence is provided for the “wild-type” SPE. Applicant has indicated that Figure 3 contains a sequence for wild type SPE-A. However, Applicant has not included said sequence in his claim language. Since, as indicated by Applicant on page 12 in Paper No. 17, there is variability between wild-type SPE-A sequences, the specification does not support the genus (all mutants derived from all possible wild type SPE-A sequences) encompassed by the rejected claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 30-47, 50-74, 77-88 and 91-99 are rejected under 35 U.S.C. 102(b) as being anticipated by Weeks et al. (Infection and Immunity, Vol. 52, No. 1, 1986, pages 144-150).

Weeks et al. disclose SPE-A molecules that, in the absence of evidence to the contrary, are commensurate in scope with the SPE-A mutants of the instant claims. It should be noted that no baseline sequence is provided for the “wild-type” SPE-A. Applicant has indicated that Figure 3 contains a sequence for wild type SPE-A. However, Applicant has not included said sequence in his claim language and therefore the claimed SPE-A mutants hence on all SPE-A species.

Claims 30-47, 50-74, 77-88 and 91-99 are rejected under 35 U.S.C. 102(b) as being anticipated by Johnson et al. (Molecular and General Genetics Vol. 203, 1986, pages 354-356).

Johnson et al. disclose SPE-A molecules that, in the absence of evidence to the contrary, are commensurate in scope with the SPE-A mutants of the instant claims. It should be noted that no baseline sequence is provided for the “wild-type” SPE-A. Applicant has indicated that Figure 3 contains a sequence for wild type SPE-A. However, Applicant has not included said sequence in his claim language and therefore the claimed SPE-A mutants hence on all SPE-A species.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert A. Zeman whose telephone number is (703) 308-7991. The examiner can normally be reached on Monday- Thursday, 7am -5:30 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on (703) 308-3909. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.



Robert A. Zeman
August 27, 2003